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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,055	09/09/2003	Kathleen Aertgeerts	SYR-DPPIV-5001-C1	3118

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,055	AERTGEERTS ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☒ Claim(s) *15 and 16* is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-23 are pending.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-16, 22, and 23, drawn to crystalline composition of dipeptidyl peptidase IV, classified in class 435, subclass 212.

II. Claims 17-21, drawn to a method of identifying compound that associate with dipeptidyl peptidase IV, classified in class 702, subclass 27.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions, the crystal composition of invention I is not utilized by the method of invention II.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with David Weitz on January 26, 2006 a provisional election was made without traverse to prosecute invention I, claims 1-16, 22 and 23. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The disclosure is objected to because of the following informalities: (a) The phrase "residues 51-778 of SEQ ID NO: 1" is found through out the specification, in claims 1-3, 7-9, and 14, and the Figures, but SEQ ID NO: 1 contains only 766 amino acid residues; (b) "Endo-F1 enzyme treatment" at page 48 paragraph 192 is not defined in the specification and it is not clear what kind of treatment is it; (c) "IMAC" at page 48, paragraph 191, the abbreviation is not defined at least once in the specification; and (c) the abbreviation TCEP at page 49 paragraph 190 is not defined any where in the specification. Appropriate correction is required.

The drawings are objected to because the headings for the sequences are wrong and the atomic coordinate date in Figure 3 is confusing. Figure 3 lists the atomic coordinate of what is believed to be a homotetremer, but, at least, subunits A and B have different amino acid residues. Subunit A starts with Arg-52 and end with Pro-778 (it should be 776), whereas subunit B start with His 47-His-50 (part of the His-tag), which is followed by Ser-51 to Pro-778 (the numbers of the amino acid residues should be corrected to corresponds to either the amino acid sequence of SEQ ID NO: 1 or 3. Finally, the abbreviation "NAG" is neither defined in the specification, figure description, or the legend of the Figure. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement-drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. 37 CFR 1.821 (d) requires the insertion of a sequence identification number following the mentioning of a protein, which its sequence is disclosed in the sequence listing. For example SEQ ID NO: 1 should be inserted in paragraph 43, line 2 and on line 1 of paragraph 45 at page 10. Figure 3 constitute a disclosure of an amino acid sequence, which the sequence identifier should be in the heading of the Table of Figure 3 description. Also, Tables 1-3 should have a sequence identifier following DPPIV. Applicants are responsible for identifying all instances that require a sequence identifier and insert them through out the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-13, 22, and 23 are directed to all possible crystals of proteins having 90% or 95%, sequence homology to residues 39-766 of SEQ ID NO: 1 of human dipeptidyl peptidase IV (DPPIV) or any protein comprising residues 39-766 of SEQ ID NO: 1 (claims 1-4), and any crystallization method to obtained any crystal of any of said DPPIV. Claims 22 and 23 read on any crystal of any DPPIV from any source in space group $P2_1$, or having cell unit dimensions a = 121.53 Angstrom, b = 124.11 Angstrom and c = 144.42 Angstrom, with alpha = gamma = 90 degrees and beta = 114. 6 degrees. In addition, the claimed crystals can be obtained from glycosylated or deglycosylated proteins. The specification, however, only provides a single representative species of these crystals, i.e., a monoclinic crystal of the amino acid sequence of SEQ ID NO: 3 in space group $P2_1$ with unit cell dimensions a = 121.53 Angstroms, b = 124.11 Angstroms, c = 144.42 Angstroms, and beta = 114.6 degrees. There is no disclosure of any particular relationship between the structure of said crystal, the amino acid sequence, the glycosylation state of the protein, and the crystallization conditions. The specification also fails to identify the glycosylation state of the crystallized protein of SEQ ID NO: 3 and to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the space group and the unit cell dimension cited in claims 22 and 23, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-13, 22, and 23 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals comprising a proteins having 90% or 95%, sequence homology to residues 39-766 of SEQ ID NO: 1 of DPPIV or any protein comprising residues 39-766 of SEQ ID NO: 1 (claims 1-4), and any crystallization method to obtained any crystal of any of said DPPIV. Claims 22 and 23 read on any crystal of any DPPIV from any source in space group $P2_1$, or having cell unit dimensions a = 121.53 Angstrom, b = 124.11 Angstrom and c = 144.42 Angstrom, with alpha = gamma = 90 degrees and beta = 114. 6 degrees. In addition, the claimed crystals can be obtained from glycosylated or deglycosylated proteins. Factors to be considered in determining whether undue

experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses all-possible crystals comprising a proteins having 90% or 95%, sequence homology to residues 39-766 of SEQ ID NO: 1 of DPPIV or any protein comprising residues 39-766 of SEQ ID NO: 1 (claims 1-4), and any crystallization method to obtained any crystal of any of said DPPIV. Claims 22 and 23 read on any crystal of any DPPIV from any source in space group $P2_1$, or having cell unit dimensions a = 121.53 Angstrom, b = 124.11 Angstrom and c = 144.42 Angstrom, with alpha = gamma = 90 degrees and beta = 114. 6 degrees. The specification provides guidance and examples in the form of an assay to prepare the polypeptide of SEQ ID NO: 3 in insect cells, which is expected to produce the protein in glycosylated form (example 1) and crystallize the protein in its glycosylated state to obtain a monoclinic crystal (example 2). While molecular biological techniques and genetic manipulation to make any protein and several mammalian DPPIV are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of proteins and their complexes as well as the crystallization of glycosylated proteins and protein comprising membrane anchoring domain is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form crystallizing is highly unpredictable. The skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. A protein which may crystallize under specific crystallization condition, it mutants may or may not crystallize under the same condition. Glycosylated proteins are in particular, are problematic because they are not homogenous in structure and protein comprising the trans membrane domains are insoluble in aqueous solution. In many cases, a protein that can't be crystallized, one of its specific mutants might be crystallizable. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein and its complexes that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystal of DPPIV from any biological source or their cystallizable mutants, and obtain a crystal suitable for structure determination by X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions or mutants which can be crystallized where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences of the DPPIV, and identify a crystallization conditions that produce a crystal suitable for structure determination by X-

ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrase "residues 51-778 of SEQ ID NO: 1" in claims 1-3, 7-9, and 14 renders the claims indefinite and confusing because SEQ ID NO: 1 contains only 766 amino acid residues. For examination purposes only, it is assumed that the applicant intended to say residues 39-776 of SEQ ID NO: 1.

(b) The abbreviation "DPPIV" in claims 22 and 23 renders the claims indefinite. Abbreviations or acronyms have to be defined at least once in the claims. For examination purposes, DPPIV is assumed to mean any dipeptidyl peptidase IV from any source.

(c) Claims 4-6 and 10-13 are included in this rejection because they are dependent from a rejected claim and do not cure its deficincies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4,7-10, and 13 rejected under 35 U.S.C. 102(e) as being anticipated by U. S. published application US 2005/0260732 ('732), which claim priority to provisional U. S. application 60/398,761, filed on July 29, 2002. The provisional applications in Japanese fully support the claimed invention.

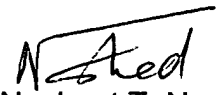
The '732 document teach the crystallization of water-soluble human dipeptidyl peptidse IV (DPPIV) residues 33-766 with a histidine-tag attached to the C-terminus, see page 14, paragraph 203. It describes an orthorhombic crystal in space group $P2_12_12_1$ under the conditions cited in paragraphs 220 and 221. The crystal of DPPIV described in the '732 document contains a protein that is more than 95% homologues to residues 51-776 of the instant application and comprises consecutively residues 51-766 (claims 1-3), and diffracts X-ray at a resolution better than 3.0 Angstroms (claim 4). The crystallization method described in paragraphs 220-222 is sufficient to obtain the crystal disclosed in '732 (claim 7-10) and the crystal is of sufficient quality to determine the three dimensional structure of DPPIV (claim 13).

Claims 15 and 16 are allowed over the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656